REMARKS/ARGUMENTS

With this amendment, claims 1, 12, 14-18, and 54-55 are pending. Claims 2-11, 13, 19-26, 28-39, and 45-53 are cancelled without prejudice to subsequent revival. Claims 27 and 40-44 are withdrawn. New claim 55 is added.

I. Status of the claims

Claim 1 is amended to recite determination of kinase activity of the Axl angiogenesis polypeptide using an in vitro assay. Support for this amendment is found throughout the specification, for example, at page 6, lines 7-20. Claim 1 is also amended to recite performance of assays in the presence and absence of the test compound. Support for this amendment is found throughout the specification, for example, at page 9, line 32 through page 10, line 4. Claim 1 is also amended to recite a step of performing a cell based angiogenesis phenotype assay using a cell that comprises the Axl angiogenesis polypeptide. Support for this amendment is found throughout the specification, for example, at page 8, lines18-24, page 30, lines 6-10 and 14-29, page 31, line 22 through page 33, line 12, and page 32, lines 25-26. Claim 1 is further amended to recite that inhibition of Axl kinase activity and inhibition of the cell-based angiogenesis phenotype assay in the presence of the compound identify the compound as an inhibitor of angiogenesis. Support for this amendment is found throughout the specification, for example, at Figures 12-17, which demonstrate that an RNAi molecule specific for the nucleic acid that encodes the Axl angiogenesis polypeptide down regulates expression of the Axl polypeptide in a cell and that down regulation and lack of expression of the Axl polypeptide causes inhibition of cell-based angiogenesis assays. As expression of the Axl polypeptide is down regulated, kinase activity of the Axl polypeptide is also necessarily down regulated in the cell. Claim 12 is amended to recite tube formation. Support for this amendment is found throughout the specification, for example, at Figure 17. New claim 55 recites that inhibition of the angiogenesis phenotype in the cell-based angiogenesis assay is caused by down regulation of expression of the angiogenesis polypeptide. Support for this amendment is found throughout the specification, for example, at Figures 12-17 These amendments add no new matter.

II. Rejections under 35 U.S.C. §112, first paragraph, enablement

A. Maintained

Claims 1-12, 14-19, and 54 are rejected for alleged lack of enablement. According to the Office Action mailed on August 23, 2006, the claims are enabled for the use of an Axl polypeptide comprising SEQ ID NO:4, but are allegedly not enabled for use of Axl polypeptides that comprise amino acid sequences with 95% identity to SEQ ID NO:4. In discussion of the Axl protein, the Office Action also alleges that little is known about that protein. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

Factors such as the amount of guidance presented in the specification and the presence of working examples must be considered to determine whether undue experimentation is required to practice the claimed invention. *See, e.g.*, *Ex Parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1985) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). As described in *Wands*, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Wands*, USPQ2d at 1404, quoting *In re Jackson*, 217 USPQ 804 (Bd. Pat. App. & Int. 1982). Moreover, "[a] patent need not teach, and preferably omits, what is well known in the art." MPEP 2164.01 *citing In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 221 USPQ 481, 489 (Fed. Cir. 1984).

As set forth in the Manual of Patent Examining Procedure (MPEP) § 2164.01, "the test of enablement is not whether any experimentation is necessary, but whether... it is undue." Further, the "fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" (citations omitted). Finally, claims reading on inoperative embodiments are enabled if the skilled artisan understands how to avoid

inoperative embodiments. *See, e.g., In re Cook and Merigold*, 169 USPQ 299, 301 (C.C.P.A. 1971).

First, claim 54 is directed to a protein that comprises SEQ ID NO:4. The Office Action has not provided reasoning for maintaining the enablement rejection of this claim. The remaining claims are directed to methods of identifying inhibitors of angiogenesis using Axl proteins with 95% identity to the full length of SEQ ID NO:4, wherein the Axl polypeptide has kinase activity and down regulation of the Axl protein results in inhibition of a cell-based angiogenesis assay. The specification provides ample support for these claims. For example, SEQ ID NO:4 is provided, and, to identify proteins with 95% identity to SEQ ID NO:4, well-known sequence analysis algorithms are disclosed at page 11, lines 15-23. Axl was known to be a tyrosine kinase at the time of filing, and therefore, Axl kinase assays can be used to easily identify Axl polypeptides that fall with the scope of the claims. The claimed methods have already identified inhibitors of the Axl polypeptide that also inhibit angiogenesis. Down regulation of the Axl polypeptide by an inhibitory molecule and the resulting inhibition of a number of cell-based angiogenesis assays is demonstrated at Figures 12-17. Based on these amendments, Applicants believe that the claims are fully enabled.

In the previous response, Applicants argued that claims are enabled and cited two decisions by the Board of Patent Appeals and Interferences: *Ex parte Sun,* Appeal No. 2003-1993 and *Ex parte Bandman*, Appeal No. 2004-2319. The present Office Action alleges that the cases are not relevant based on alleged differences in the fact patterns. Applicants disagree and assert that both *Sun* and *Bandman* require an Examiner to base a rejection for alleged lack of enablement on a specific explanation or evidence of why the claimed molecule would not maintain an asserted activity after mutation of, *e.g.*, 5% of the amino acid sequence. *Sun* at page 7 and *Bandman* at page 15. Applicants have SEQ ID NO:4, and, to identify proteins with 95% identity to SEQ ID NO:4, well-known sequence analysis algorithms are disclosed at page 11, lines 15-23. Axl was known to be a tyrosine kinase at the time of filing, and angiogenesis assays that are regulated by Axl are disclosed and demonstrated. The Office Action has not provided sufficient analysis or evidence to demonstrate that one of skill, using the information in the

specification and literature at the time of filing, would not be able to make and use the genus of Axl polypeptides with 95% identity to SEQ ID NO:4. Therefore, the Office Action has not met its burden in making the enablement rejection.

B. New rejections

Claims 1-12, 14-19, and 54 are rejected for alleged lack of enablement because the specification allegedly does not provide a "nexus" between down regulation of the Axl polypeptide and angiogenesis. The Office Action appears to indicate that enablement is provided for claims that include a step of determining inhibition of the angiogenesis polypeptide by the compound. Office Action at page 15. In order to expedite prosecution, Applicants have amended claim 1 to include such a step, *i.e.*, inhibition of a cell-based angiogenesis phenotype assay in the presence of the compound.

In view of the above amendments and remarks, withdrawal of the rejections for alleged lack of enablement is respectfully requested.

III. Rejections under 35 U.S.C. §112, first paragraph, written description

Claims 1-12, 14-19, 27-37, 40-44, 45 and 53 are rejected for allegedly failing to meet the written description requirement. According to the Office Action the specification does not describe the genus of Axl polypeptides used in the claimed methods. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

As currently applied, the specification does comply with US patent law for description of a nucleic acid or amino acid sequence. The Federal Circuit court of Appeals addressed the description adequate to show one of skill that the inventors were in possession of a claimed genus at the time of filing. *See, e.g., Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002). An applicant may also show that an invention is complete by

> . . . disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention . . . *i.e.*, complete or partial structure, other physical and/or

> chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. *Id.* at 1613.

Furthermore, "description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces." *See, e.g.*, 66 Fed. Reg. 1099, 1106 (2001).

The specification does provide descriptive support for the full scope of the claimed invention by providing both SEQ ID NO:4, a reference sequence for the recited polypeptides, and assays for regulation and inhibition of angiogenesis. Axl kinase activity was well-known at the time of filing. The assays are described throughout the specification, for example, regulation and modulation of angiogenesis (at page 1,line 33 through page 2, line 3; page 2, lines 24-28; page 5, lines 3-21; page 6, lines 8-9; page 32, lines 25-32; page 33, lines 15-26; and page 48, lines 23-30; and Figures 11-17), haptotaxis assays, (at page 32, lines 28-32; page 48, lines 25-30; and Figures 11-13), endothelial tube formation assays, (at page 32, lines 28-32 and Figure 17), chick CAM assays (at page 33, lines 17-22), mouse corneal assays (page 33, lines 23-26) and tumor neovascularization assays (at page 33, lines 27-31; page 49, lines 1-20; and Figure 18). This information is more than adequate to meet the written description requirement, particularly in view of *Enzo*, cited above, recent Board decisions, and the interpretation of the Written Description Guidelines evidenced by the USPTO's own Synopsis of Application of Written Description Guidelines.

In the previous response, Applicants argued that claims are described and cited again *Sun* and *Bandman*. The present Office Action alleges that the cases are not relevant based on alleged differences in the fact patterns. Applicants disagree and assert that both *Sun* and *Bandman* require an Examiner to base a rejection for alleged lack of written description on a specific explanation or evidence of why the claimed molecule would not maintain an asserted activity after mutation of, *e.g.*, 5% of the amino acid sequence. *Sun* at page 9 and *Bandman* at page 5. In particular, the Board in Sun indicated that identification of conserved areas of a protein and functions of those areas sufficiently supports a claim to a genus of polypeptides with

80% identity to the reference sequence. Sun at page 10. Similar information is provided in Figure 11, which discloses Ig binding regions FN3 regions and the tyrosine kinase domain of the Axl protein. According to Sun, this type information is sufficient to provide descriptive support of the claimed genus.

The Office Action also disputes that Example 14 of the Synopsis of Application of Written Description Guidelines applies to the claims. In response, Applicants assert that the amended claims recite kinase activity of the Axl protein and an assay for inhibition of an angiogenesis phenotype caused by the inhibition of the Axl protein. The Synopsis indicates that a "single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay. . . " that could be used to identify members of the claimed genus. The amended claims thus follow the guidelines for written description put forth by the US Patent Office.

In view of the above arguments and amendments, withdrawal of the rejection for alleged lack of written description is respectfully requested.

IV. Rejections under 35 U.S.C. §102

Claims 1, 2, 5, 6, 9-11, 14, 19 and 54 are rejected as allegedly anticipated by Healey *et al., Am .J. Physiol. Lung Cell Mol. Physiol.* 280:L1273-L1281 (2001). As amended, independent claim 1 is directed to a method of identifying a compound that inhibits angiogenesis, by determining kinase activity of Axl polypeptide that has 95% identity to a reference sequence in the presence and absence of the compound. In addition, a cell-based angiogenesis assay is performed using an endothelial cell that comprises the Axl polypeptide. Compounds that inhibit kinase activity of the Axl angiogenesis polypeptide and that inhibit a cell-based angiogenesis assay are identified as inhibitors of angiogenesis.

To anticipate a claim, the reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found...in a single prior art reference." *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Thus, in order to anticipate, the cited reference must contain every

element of the claims at issue. The cited references do not. Therefore, to the extent the rejection applies to the amended claims, Applicants traverse the rejection.

According to the Office Action Healey *et al.* disclose a method of identifying a compound that inhibits angiogenesis through the Axl polypeptide by contacting a cell that comprises the Axl polypeptide with the Gas-6 protein. Gas-6 is a ligand for the Axl polypeptide. The Office Action agrees that Healy *et al.* does not teach that Gas-6 inhibits angiogenesis. However, the Office Action cites a second reference, Gallicio *et al. Blood* 105:1970-1976 (2005) as allegedly demonstrating that Gas-6 interaction with Axl polypeptide inhibits angiogenesis and, therefore, that Healy *et al.* inherently anticipate that claimed invention. Applicants dispute the Office Action's findings with respect to the disclosure of Gallicio *et al.*

Healey *et al.* does not inherently disclose that inhibition of the Axl polypeptide causes inhibition of angiogenesis as is claimed, even in view of the disclosure of Gallicio *et al.* With regard to inherent anticipation of a particular feature, an undisclosed element anticipates only if it is necessarily present in the cited reference. *Schering Corp. v. Geneva Pharmaceuticals, Inc.* 67USPQ2d 1664, 1667 (Fed. Cir. 2003), *citing Continental Can Co. v. Monsanto Co.* 20 USPQ2d 1746 (Fed. Cir. 1991). Gallicio *et al.* is silent as to inhibition or down regulation of the Axl polypeptide and its effect on angiogenesis.

Gallicio *et al.* discloses that Gas-6 **stimulates** the Axl polypeptide, which inhibits activation of vascular endothelial growth factor receptor 2 (VEGF-R2), which, thus, **inhibits activation** of an angiogenic program in vascular endothelial cells. Based on the results of Gallicio *et al.*, those of skill would predict that **inhibition** of the Axl peptide would activate VEGF-R2 and **stimulate activation** of an angiogenic program in vascular endothelial cells. At a minimum, those of skill would predict that inhibition of the Axl polypeptide would have little or no effect on an angiogenesis program based on the results of Gallicio *et al.*

In contrast, the claims are direct to identification of an inhibitor of angiogenesis using a method that includes a step of identifying a compound that **inhibits** Axl kinase activity and **inhibits** a cell-based angiogenesis phenotype assay (or program) in an endothelial that comprises the Axl polypeptide. Gallicio *et al.* provides no disclosure that inhibition of the Axl

polypeptide will result in inhibition of angiogenesis and does not support the inherent anticipation rejection of the claims based on Healy *et al.* Therefore, the cited reference does not expressly or inherently disclose all the elements of the claimed invention and cannot anticipate the claims.

In view of the above amendments and arguments, withdrawal of the rejection for alleged anticipation is respectfully requested.

V. Rejections under 35 U.S.C. §103(a)

Claims 12, and 15-18 are rejected as allegedly obvious over Healey *et al.* in view of Varner and Cherish, *Cell Biology* 8:724-730 (1996); Panzer *et al.* US Patent Application Publication 2004/0048253 (2001); and Ruoslahti *et al.* US Patent No. 6,180,084 (2001). To the extent the rejection applies to the amended claims, Applicants traverse the rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claims limitations. MPEP§2143. See also *In re Rouffet,* 47 USPQ2d 1453. The court in *Rouffet* stated that "even when the level of skill in the art is high, the Board must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination." *Rouffet* at 1459. The court has also stated that actual evidence of a suggestion, or teaching, or motivation to combine is required and the showing of a suggestion, or teaching, or motivation to combine must be "clear and particular." *In re Dembiczak,* 50 USPQ2d 1614, 1617 (1999). Under the standards listed above, the Office Action does not establish a prima facie case of obviousness.

Claims 12 and 15-18 depend from claim 1, which is discussed above. The Office Action applies the analysis discussed above to Healey *et al.* The Office Action asserts that Varner and Cherish disclose that integrin $\alpha v\beta 3$ is significantly upregulated on vascular cells and plays a biological role in blood vessel formation and that Panzer *et al.* and Ruoslahti *et al.* teach

general method of screening compounds for a desired effect. The cited references do not disclose all the elements of the claimed invention, do not provide motivation for combination of the references and do not provide an expectation of success in arrival at the claimed invention by combining the references.

Healey *et al.* teaches away from the claimed use of the Axl polypeptide to identify compounds that inhibit angiogenesis. Applicants assert that Healey *et al.* teaches only that Axl and its ligand Gas-6 have anti-apoptotic activity in the tested human pulmonary artery endothelial cells (HPAEC). Healey *et al.* disclose that the antiapoptotic activities of Gas-6 are "relevant to endothelial cell survival in the quiescent environment of the vessel wall." *See, e.g.*, Healey *et al.* abstract at page L1273. Thus, according to Healey *et al.* Gas-6 activation of the Axl protein is used to promote endothelial cell survival when angiogenesis is not occurring. Therefore, Healey *et al.* does not teach or suggest use of the Axl polypeptide to identify compounds that inhibit angiogenesis.

The Office Action alleges that Varner and Cherish disclose a role for integrin $\alpha v\beta 3$ in angiogenesis. However, Varner and Cherish do not teach or suggest a role for Axl in angiogenesis and, therefore, cannot be used to cure the deficiencies of Healey *et al.* The other cited references, Panzer *et al.*, and Ruoslahti *et al.* disclose only general methods of screening small molecules and other compounds for a desired effect. No discussion of the Axl polypeptide or a role in angiogenesis is disclosed. Panzer *et al.*, and Ruoslahti *et al.* cannot be used to cure the deficiencies of Healey *et al.*

The Office Action fails to provide any motivation for those of skill to combine the cited references. Taken together, those of skill could only be motivated to assay apoptosis as regulated by Gas6 and Axl, and the Office Appears to believe that this can be done by measuring surface $\alpha v\beta 3$ levels in the presence of various compounds. The invention is based on the novel recognition that inhibition of the Axl polypeptide inhibits angiogenesis. None of the references disclose that Axl has any role in angiogenesis, and out of the 1000's of proteins expressed by an endothelial cell, none of the references suggest inhibition of the Axl protein as a method to inhibit angiogenesis. Again, the combined references direct those of skill to analyze apoptosis,

not angiogenesis. Without the recognition that inhibition of the Axl polypeptide inhibits angiogenesis, the references cannot provide motivation for combination of the references and cannot provide an expectation of success in arrival at the claimed invention by combining the references. In addition, without the recognition that inhibition of the Axl polypeptide inhibits angiogenesis, the combined references do not disclose all the elements of the claimed invention. Thus, alone or in combination, the cited references cannot be used to provide a prima facie case of obviousness.

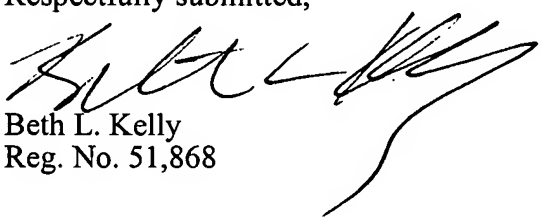
In view of the above arguments and amendments, withdrawal of the rejection for alleged obviousness is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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